

# Improved oral absorption of cilostazol via sulfonate salt formation with mesylate and besylate

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**Objective:** Cilostazol is a Biopharmaceutical Classification System class II drug with low solubility and high permeability, so its oral absorption is variable and incomplete. The aim of this study was to prepare two sulfonate salts of cilostazol to increase the dissolution and hence the oral bioavailability of cilostazol.

**Methods:** Cilostazol mesylate and cilostazol besylate were synthesized from cilostazol by acid addition reaction with methane sulfonic acid and benzene sulfonic acid, respectively. The salt preparations were characterized by nuclear magnetic resonance spectroscopy. The water contents, hygroscopicity, stress stability, and photostability of the two cilostazol salts were also determined. The dissolution profiles in various pH conditions and pharmacokinetic studies in rats were compared with those of cilostazol-free base.

**Results:** The two cilostazol salts exhibited good physicochemical properties, such as nonhygroscopicity, stress stability, and photostability, which make it suitable for the preparation of pharmaceutical formulations. Both cilostazol mesylate and cilostazol besylate showed significantly improved dissolution rate and extent of drug release in the pH range 1.2–6.8 compared to the cilostazol-free base. In addition, after oral administration to rats, cilostazol mesylate and cilostazol besylate showed increases in  $C_{max}$  and  $AUC_t$  of approximately 3.65- and 2.87-fold and 3.88- and 2.94-fold, respectively, compared to cilostazol-free base.

**Conclusion:** This study showed that two novel salts of cilostazol, such as cilostazol mesylate and cilostazol besylate, could be used to enhance its oral absorption. The findings warrant further preclinical and clinical studies on cilostazol mesylate and cilostazol besylate at doses lower than the usually recommended dosage, so that it can be established as an alternative to the marketed cilostazol tablet.

**Keywords:** BCS class II, cilostazol, besylate, mesylate, acid addition reaction, dissolution

## Introduction

Cilostazol is an antiplatelet drug with peripheral vasodilatory effects, which selectively inhibits phosphodiesterase III with a resultant increase in intracellular cyclic adenosine monophosphate concentrations in platelets and blood vessels.<sup>1</sup> This drug is marketed as oral tablets under the trade name Pletal® (Otsuka Pharmaceutical, Tokyo, Japan) with a recommended dosage of 100 mg twice per day. Cilostazol is a weak basic molecule ( $pK_a$ , 11.8), which is slightly soluble in methanol, ethanol, and practically insoluble in water.<sup>2</sup> It is categorized as a Biopharmaceutical Classification System class II drug with high permeability and low solubility.<sup>3</sup> Therefore, cilostazol absorption in the gastrointestinal tract is slow, variable, and incomplete,<sup>4</sup> which may explain the limited and inconsistent pharmacological effects of cilostazol. The oral absorption of Biopharmaceutical Classification System class II drugs can be improved by increasing their solubility and dissolution.<sup>5–7</sup> A number of techniques have been reported to increase

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the aqueous solubility of poorly soluble drugs,<sup>8</sup> such as salt formation,<sup>9</sup> micronization, the solid dispersion technique, and emulsification. Various formulations of cilostazol have been examined to overcome the problems outlined above, such as using  $\beta$ -cyclodextrin inclusion complex,<sup>10,11</sup> nano-sized crystalline particles,<sup>12</sup> formation of nanoemulsions,<sup>13–15</sup> microemulsions,<sup>16</sup> and spray-dried solid dispersions.<sup>17</sup> However, to our knowledge, there have been no previous studies regarding salt formation of cilostazol.

Salt formation of weakly acidic or basic drugs has been widely used to improve aqueous solubility or dissolution rates because of its high suitability for pharmaceutical development, such as low toxic potential and ease of manufacture.<sup>9</sup> Thus, for cilostazol, salt formation with the acidic counter-ion could also be a beneficial approach to improve dissolution and oral absorption. Sulfonic acid is one of the most commonly used pharmaceutically acceptable acidic counterions.<sup>8,9,18</sup> Sulfonic acid salts, particularly alkyl sulfonates such as mesylate and besylate, generally result in a high melting point, which is important both from the viewpoint of processability and stability, and good aqueous solubility, which is important from a biopharmaceutical perspective.<sup>18–20</sup>

Therefore, this study was performed to examine the effects on the oral bioavailability of cilostazol of preparation of the salt forms, cilostazol mesylate and cilostazol besylate, by acid addition reaction using methane sulfonic acid and benzene sulfonic acid. Both in vitro dissolution studies and in vivo pharmacokinetic studies in rats of cilostazol mesylate and cilostazol besylate were performed to clarify the enhanced oral bioavailability of cilostazol using these salts.

## Materials and methods

### Materials

Cilostazol-free base, benzene sulfonic acid (besylate), methane sulfonic acid (mesylate), chlorpropamide, dimethylsulfoxide, formic acid, polyethylene glycol 400, and Tween 80 were purchased from Sigma-Aldrich (St Louis, MO, USA). All solvents were of high-performance liquid chromatography (HPLC) grade and were obtained from Burdick and Jackson Company (Morristown, NJ, USA), and other chemicals were of the highest quality available.

### Preparation of cilostazol two salts

Methane sulfonic acid or benzene sulfonic acid (1.2 mmol) was added to a stirred solution of cilostazol (370 mg, 1.0 mmol) in chloroform (10 mL) at 25°C, and the mixture was stirred at the same temperature for 12 hours. The solvent was then removed under reduced pressure, and diethyl ether

(10 mL) was added to the residue and stirred for 1 hour at 25°C. The resulting triturated solid was filtered and dried at 40°C under reduced pressure to give the cilostazol salt. The nuclear magnetic resonance (NMR) spectra were obtained (AVANCE III 500 MHz; Bruker, Billerica, MA, USA) using residual undeuterated solvent or tetramethylsilane as an internal reference. Chemical shift values ( $\delta$  units) were interpreted for confirmation.

### Determination of water contents in cilostazol salts

The water contents in cilostazol mesylate and cilostazol besylate were determined using a Karl Fischer Moisture Titrator MKA-520 (Kyoto Electronics Manufacturing Co., Ltd., Kyoto, Japan).

### Hygroscopicity

Hygroscopicity was determined according to the method proposed by Callahan et al with some modifications. The two cilostazol salts were uniformly spread as a thin layer in a Petri dish and kept in sealed desiccators at 25°C in the different humidity conditions:<sup>21</sup> 22% relative humidity (RH; silica gel) and 92.5% RH (saturated solution of potassium nitrate). At each investigated RH, samples were prepared in triplicate. After 1 week, the samples were weighed, and hygroscopicity was expressed as gram of adsorbed moisture per 100 g dry solids (g/100 g).

### Stability testing

For stress stability study, ~2 mg of each cilostazol salt was placed in an amber glass bottle. The samples were stored at 40°C $\pm$ 2°C/75% $\pm$ 5% RH and at 60°C $\pm$ 2°C for 6 weeks in a stability chamber (Labcare Pvt. Ltd., Mumbai, India). After storage, samples were evaluated for purity as described in the “Cilostazol determination in salts” section.

For photostability testing, ~2 mg of the two cilostazol salts were spread in a clear glass bottle. The samples were placed inside a light exposure chamber (SUNTEST CPS+, Atlas Material Testing Technology, LLC, Chicago, IL, USA) where temperature was maintained at 25°C. The light source is a xenon arc lamp filtered through window glass to mimic indoor daylight. The total light exposure (300–800 nm wavelength) was 200 W/m<sup>2</sup> for 24 hours. Control samples, which were protected with aluminum foil, were also placed in the light cabinet and exposed concurrently. Following removal from the light cabinet, all samples were prepared for analysis as described in the “Cilostazol determination in salts” section.

## In vitro dissolution study

Dissolution tests<sup>22</sup> for cilostazol-free base, cilostazol mesylate, and cilostazol besylate were carried out in triplicate at  $37^{\circ}\text{C}\pm 0.5^{\circ}\text{C}$  using the basket method in a dissolution tester (708-DS; Agilent Technologies, Santa Clara, CA, USA). Hard gelatin capsules, “5” size (Capsugel, Morristown, NJ, USA), were filled with the accurately weighed samples equivalent to 20.0 mg of cilostazol. The dissolution medium (pH 1.2, 4.5, and 6.8 buffer) consisted of 900 mL, and the baskets were rotated at 100 rpm. Samples of 1 mL of each dissolution medium were collected at predetermined time intervals (0.25, 0.5, 1, 2, 4, and 6 hours) and replaced with an equal volume of fresh medium. The collected samples were filtered through polytetrafluoroethylene syringe filters (0.45  $\mu\text{m}$ ). After the appropriate dilution of filtrate with methanol, the amount of dissolved cilostazol was analyzed by HPLC method as described in the “Cilostazol determination in salts” section. The dissolution experiments were conducted in triplicate, and the mean values are reported.

## Cilostazol determination in salts

Cilostazol was determined using an HPLC system (Agilent 1260; Agilent Technologies) consisting of a ultraviolet detector (G1314B), a quaternary pump (G1311B), an autosampler (G1367E), and a column compartment (G1316A). The mobile phase consisted of distilled water and acetonitrile (45:55, v/v), and the flow rate was 1.0 mL/min. The wavelength of the ultraviolet detector was set at 257 nm and a reversed-phase column (Gemini C<sub>18</sub> 150 mm  $\times$  4.6 mm, 5  $\mu\text{m}$  particle size; Phenomenex, Torrance, CA, USA) was used. The column temperature was maintained at 30°C.

## Pharmacokinetic study

Male Sprague Dawley rats (8 weeks old, 250–270 g) were purchased from Orient Bio (Sungnam, Gyeonggi-do, South Korea). The protocol for the animal study was approved by the Institutional Animal Care and Use Committee on the Sungsim Campus of The Catholic University of Korea (Approval No 2014-027; Bucheon, Gyeonggi-do, South Korea). All rats were allowed free access to water and fasted for 12 hours before the drug administration. The carotid arteries (for blood sampling) of the rats were cannulated with a polyethylene tube (Clay Adams, Franklin Lakes, NJ, USA). The rats were divided into three groups ( $n=8$  per group) and orally given cilostazol-free base (20 mg/kg), cilostazol mesylate, or cilostazol besylate (equivalent to 20 mg/kg of cilostazol-free base). The free base and the two cilostazol salts were suspended in 5% Tween 80:

polyethylene glycol 200: distilled water =50:10:40 v/v/v). The suspension of each formulation (5 mL/kg) was given to rats by oral gavage. Samples of ~0.12 mL of blood were collected from each rat via the carotid artery at 0 (control), 5, 15, 30, 45, 60, 90, 120, 240, 360, 480, 600, and 720 minutes after oral administration. The cannula was flushed immediately with a heparinized 0.9% NaCl-injectable solution (20 units/mL, 0.3 mL) after taking each blood sample to prevent blood clotting. The blood samples were immediately centrifuged at 13,000 rpm for 10 minutes at 4°C, and plasma samples (50  $\mu\text{L}$ ) were stored at  $-80^{\circ}\text{C}$  until liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analysis. After the experiments, the rats were euthanized with CO<sub>2</sub>.

## Determination of cilostazol in rat plasma by LC-MS/MS

The plasma concentrations of cilostazol were determined simultaneously by a slight modification of the LC-MS/MS methods reported previously.<sup>23</sup> The LC-MS/MS system consisted of a Shimadzu Nexera HPLC system coupled with a Shimadzu LCMS-8050 triple quadrupole mass spectrometer (Shimadzu Corporation, Kyoto, Japan). Briefly, cilostazol and the internal standard (chlorpropamide, 500 ng/mL) were extracted from rat plasma (50  $\mu\text{L}$ ) using 1 mL of tert-butyl methyl ether. Chromatographic separation was performed on an ACE 3 C8 column (50 mm  $\times$  4.6 mm, 3  $\mu\text{m}$  particle size; Hichrom, Reading, Berkshire, UK) with an isocratic mobile phase consisting of distilled water and acetonitrile containing 0.1% formic acid (25:75, v/v) at a flow rate of 0.7 mL/min. The total run time was 5.0 minutes per sample. Detection and quantification were performed using a mass spectrometer in selected reaction-monitoring mode with positive electrospray ionization at  $m/z$  370.45 $\rightarrow$ 288.1 for cilostazol and  $m/z$  277.05 $\rightarrow$ 111.05 for chlorpropamide. The optimized mass spectral data were acquired under the following conditions: nitrogen was used as the nebulizing gas and drying gas at flow rates of 3.0 L/min and 10.0 L/min, respectively; the interface voltage was set to 4.5 kV; desolvation line temperature was 250°C; and the heat block temperature was 400°C. The collision energies were 18 V for cilostazol and 20 V for chlorpropamide. Argon gas was used as the collision-induced dissociation gas at a pressure of 270 kPa, with the detector voltage set to 1.72 kV. The linear range of concentration for cilostazol was 5–2,000 ng/mL, with a lower limit of quantification of 5 ng/mL. The coefficients of variation for the precision and accuracy of the assay met the acceptance criteria for bioanalyses. The intra- and

interday precision (n=5) of the assay ranged from 5.91% to 10.1%, and the intra- and interday accuracies (n=5) ranged from 88.9% to 105.4%. Cilostazol was stable under various storage and handling conditions, and no relevant crosstalk or matrix effects were observed.

## Pharmacokinetic analysis and statistical analysis

Pharmacokinetic parameters were calculated using WinNonlin software (version 5.2; Pharsight Corporation, Mountain View, CA, USA) with a noncompartment model. The times to reach maximum plasma concentration ( $T_{max}$ ) and peak plasma concentration ( $C_{max}$ ) were obtained from the measured values. The area under the concentration–time curve from time zero to the last observed time point ( $AUC_t$ ) was calculated using the linear trapezoidal rule. The relative bioavailabilities ( $F$ ) of the two cilostazol salts were calculated as:

$$F = \frac{AUC_{t, \text{cilostazol salt}}}{AUC_{t, \text{cilostazol-free base}}} \times 100\%.$$

Statistical analyses were performed using Duncan's multiple range test in SPSS a posteriori analysis of variance among the three means for the unpaired data (Version 22; SPSS Inc., Chicago, IL, USA). All results are expressed as mean  $\pm$  standard deviation (SD), except medians (ranges) for  $T_{max}$ . In all analyses,  $P < 0.05$  was taken to indicate statistical significance.

## Results and discussion

### Preparation of cilostazole mesylate or besylate salts

As mentioned earlier, cilostazol is a weak basic drug with a  $pK_a$  of 11.8 (Figure 1A). In this study, acidic counterions such as mesylate ( $pK_a$ , -1.2)<sup>9</sup> and besylate ( $pK_a$ , 0.7)<sup>9</sup> were selected for cilostazol salt because of their biopharmaceutical advantages and clinical usage as orally administered salts. The two cilostazol salts, cilostazol mesylate and cilostazol besylate, were prepared by acid addition reaction method. Both cilostazol mesylate and cilostazol besylate (Figure 1B and C) were easily prepared by mixing cilostazol with a slight excess of the corresponding sulfonic acid in chloroform, followed by trituration in diethyl ether. The salt formation of cilostazol was confirmed by <sup>1</sup>H NMR spectroscopy (Figures 2A–C). <sup>1</sup>H NMR of cilostazol mesylate showed a methyl peak of mesylate at 2.99 ppm in integral of three hydrogens, which indicated that salt formation occurred in

a 1:1 ratio between cilostazol and methane sulfonic acid (Figure 2B). The same ratio was observed in <sup>1</sup>H NMR of cilostazol besylate (Figure 2C). The cilostazol mesylate and cilostazol besylate were obtained as white powders with the reaction yield of 69% and 98%, respectively. Karl Fischer titration confirmed very low water contents of only 0.17% and 0.14% for cilostazol mesylate and cilostazol besylate, respectively. Thus, two cilostazol salts may be indicated as anhydrous forms with no water content.

### Hygroscopicity

Low hygroscopicity of a chemical compound is a very important property required for a raw material of a pharmaceutical product because it determines manufacturing and storage of the actual pharmaceutical product. The moisture contents of cilostazol mesylate were 0.32% and 4.82% at 22% RH and 92.5% RH, respectively (data not shown). The corresponding values for cilostazol besylate were 0.26% and 1.37% (data not shown). Its nonhygroscopicity was represented as a <20% (w/w) increase in moisture content above 90% RH in 1 week.<sup>24</sup> Thus, the two cilostazol salts may be regarded as nonhygroscopic compounds.

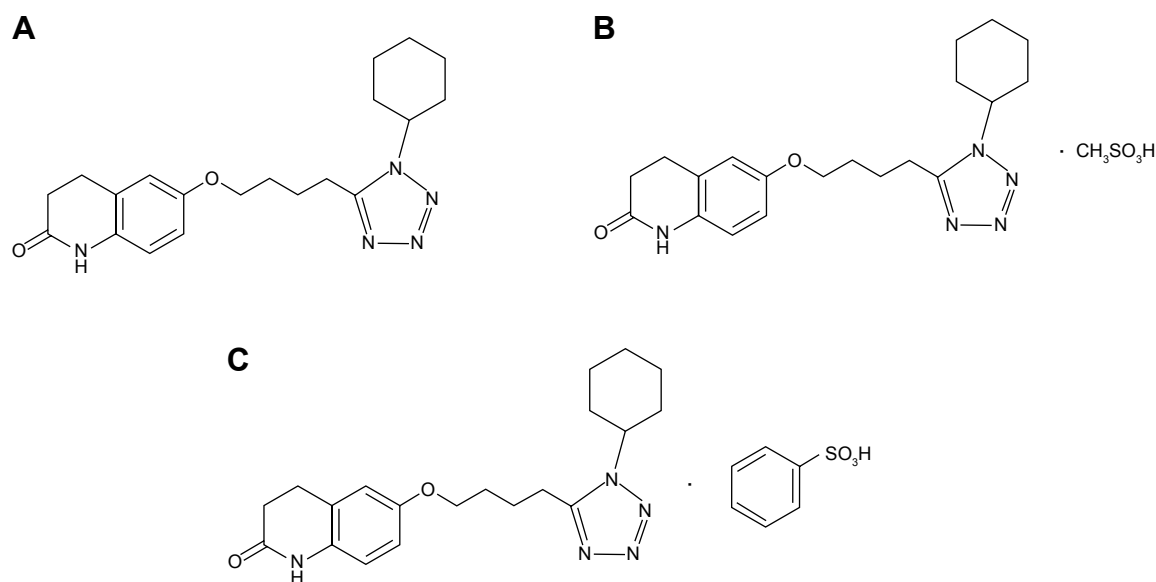
### Stability testing

Stress stability testing of the two cilostazol salts was performed under accelerated conditions (40°C $\pm$ 2°C/75% $\pm$ 5% RH and 60°C $\pm$ 2°C) for 6 weeks to clarify the influence of salt formation on chemical stability. Additionally, these formulations were exposed to light to determine the effect of irradiation on the stability of the two cilostazol salts for 24 hours.

The results of the stability tests are summarized in Table 1. All tested samples in the solid states remained colorless. Both cilostazol mesylate and cilostazol besylate exhibited good thermal stability after storage, with a recovery of more than 98.6% of the initial amount in both cases (Table 1). The two cilostazol salts were also stable after light exposure without any photodegradation (Table 1).

### In vitro dissolution study

In vitro dissolution of cilostazol-free base, cilostazol mesylate, and cilostazol besylate was carried out in HCl buffer (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 6.8) to simulate the gastrointestinal conditions. Dissolution profiles were presented in Figure 3. For cilostazol-free base, the percent cumulative drug dissolved at 6 hours was 25.4% $\pm$ 3.56%, 8.54% $\pm$ 1.89%, and 2.74% $\pm$ 0.341% in pH 1.2, 4.5, and 6.8, respectively, indicating that cilostazol exhibited

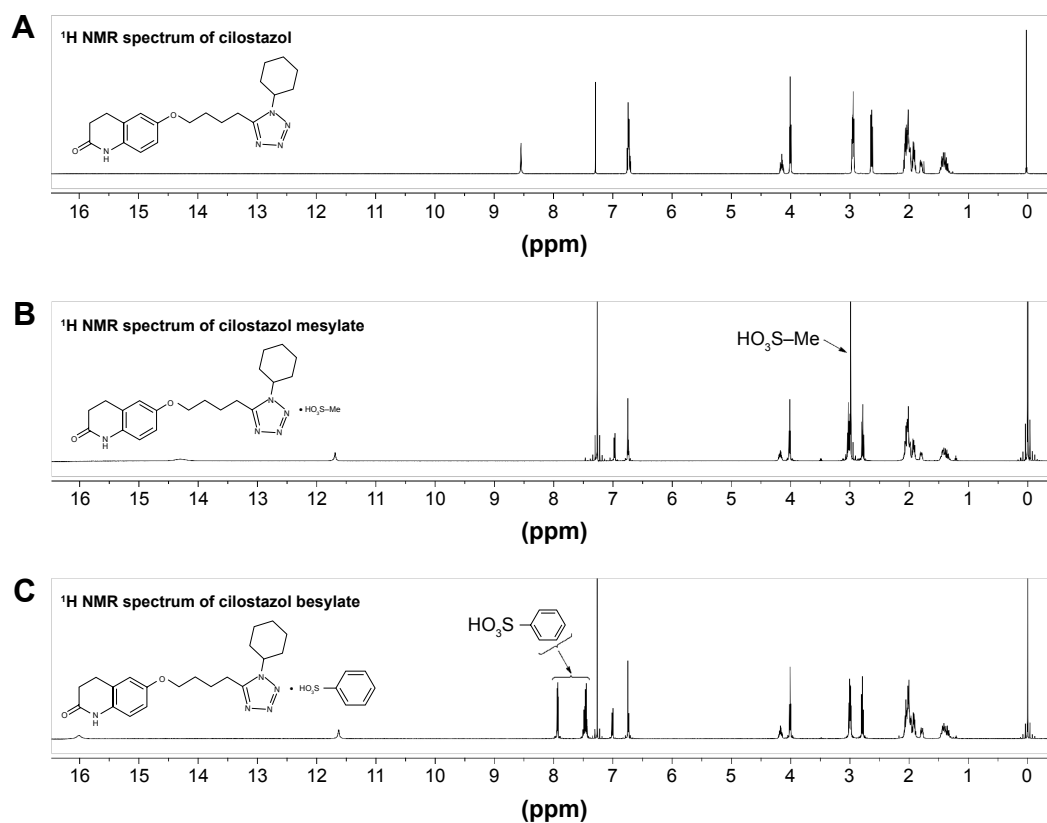


**Figure 1** Chemical structures of cilostazol (A), cilostazol mesylate (B), and cilostazol besylate (C).

a pH-dependent dissolution profiles. The lower drug dissolution obtained at higher pH values was due to the basic nature of cilostazol, which is more soluble at lower pH values.

The two cilostazol salts showed significantly improved dissolution rates and extents of drug release in 6 hours compared

to cilostazol-free base in all tested dissolution media. As shown Figure 3A, cilostazol-free base released  $25.4\% \pm 3.56\%$  of drug in HCl buffer (pH 1.2) at 6 hours, while cilostazol mesylate and cilostazol besylate showed higher levels of cilostazol dissolution ( $93.5\% \pm 6.54\%$  and  $98.6\% \pm 5.65\%$ ,



**Figure 2**  $^1\text{H}$  NMR spectra of cilostazol (A), cilostazol mesylate (B), and cilostazol besylate (C).  
**Abbreviation:** NMR, nuclear magnetic resonance.

**Table 1** The stress stability and photostability of cilostazol-free base, cilostazol mesylate, and cilostazol besylate

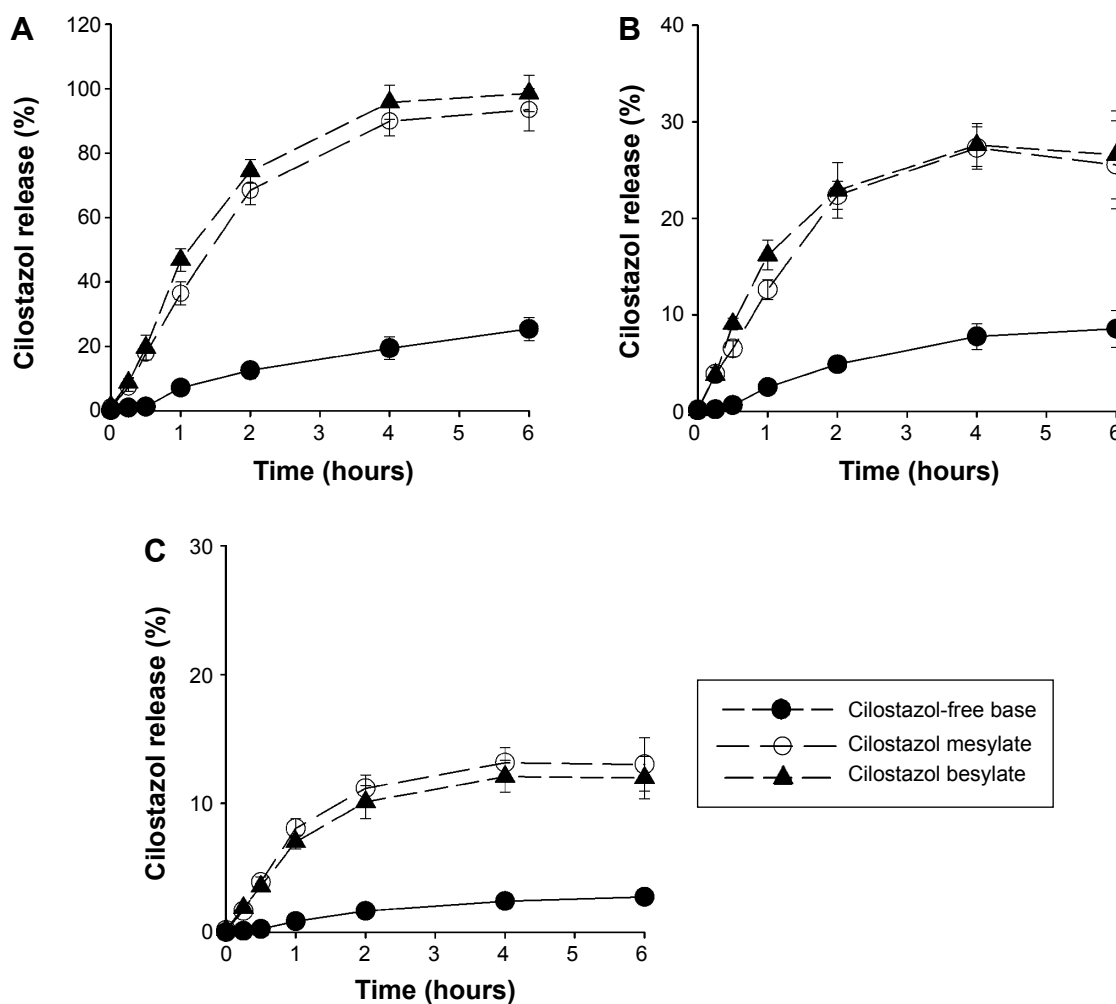
Salts	Stress stability for 6 weeks % of cilostazol remaining <sup>a</sup>		Photostability for 24 hours <sup>b</sup> % of cilostazol remaining <sup>a</sup>	
			Exposed <sup>c</sup>	Control <sup>d</sup>
	40°C/75% RH	60°C closed		
Cilostazol-free base	101±0.782	99.3±0.531	99.7±1.01	100±2.17
Cilostazol mesylate	98.9±1.10	98.6±0.620	100±2.04	101±1.58
Cilostazol besylate	100±0.891	99.4±0.487	101±1.93	101±1.65

**Notes:** Each value represents the mean ± SD (n=3). <sup>a</sup>Remaining to initial sample. <sup>b</sup>UV and visible light irradiation (200 W/m<sup>2</sup>). <sup>c</sup>The exposed samples were placed in the light cabinet. <sup>d</sup>The control samples were protected by aluminum foil, placed in the light cabinet, and exposed concurrently.

**Abbreviations:** RH, relative humidity; SD, standard deviation.

respectively) in the same time. There was no significant difference in dissolution between cilostazol mesylate and cilostazol besylate ( $P>0.05$ ). In pH 4.5 and 6.8 dissolution media, the drug released from cilostazol-free base at 6 hours, 8.54%±1.89%, and 2.74%±0.341%, respectively, owing to the lower dissolution at higher pH solution. In contrast, the drug release was greatly improved by cilostazol mesylate

(cilostazol besylate) to 25.6%±4.57% (26.6%±4.54%) in pH 4.5 buffer and 13.0%±2.07% (12.1%±1.65%) in pH 6.8 buffer in the same time (Figure 3B and C). Thus, both cilostazol mesylate and cilostazol besylate were demonstrated to markedly increase the dissolution rate and extent of drug release over the pH range of 1.2–6.8. After dissolving cilostazol salts, the pH values of the respective test media did not change.



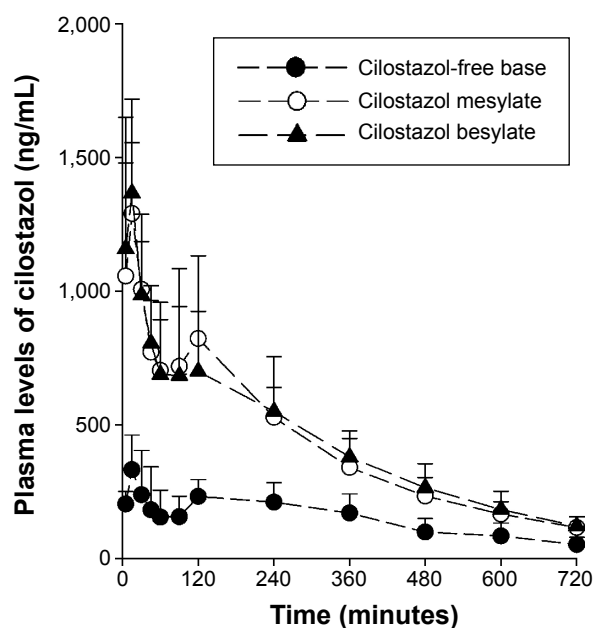
**Figure 3** Dissolution profiles of cilostazol-free base (●), cilostazol mesylate (○), and cilostazol besylate (▲) in (A) pH 1.2, (B) pH 4.5, and (C) pH 6.8 buffer media at 37°C±0.5°C (mean ± SD, n=3).

## Pharmacokinetic study

The plasma concentration–time profiles of cilostazol after oral administration of cilostazol-free base, cilostazol mesylate, and cilostazol besylate to rats are shown in Figure 4. The plasma concentrations of cilostazol in the cilostazol mesylate and besylate groups were considerably higher than those in the cilostazol-free base group at all time points examined ( $P < 0.05$ ). The  $AUC_t$  and  $C_{max}$  values for cilostazol mesylate and cilostazol besylate were higher by 2.87- and 3.65-fold and by 2.94- and 3.88-fold, respectively, than those for cilostazol-free base (Table 2). The plasma concentration profile for cilostazol mesylate was comparable to that for cilostazol besylate, and there were no significant differences in  $AUC_t$  or  $C_{max}$  between the two salt groups. In addition, the cilostazol mesylate and cilostazol besylate groups showed more rapid oral absorption and shorter  $T_{max}$  compared to the cilostazol-free base group, although they were not significantly different due to the high degrees of variability among rats (Table 2). However, there were no significant differences in terminal half-life of cilostazol among the three groups (Table 2). The in vivo oral absorption and bioavailability of cilostazol-free base were markedly enhanced by the salt formation with no notable change in the biological half-life. These in vivo pharmacokinetic results seemed to reflect the in vitro dissolution results. The enhanced oral absorption of cilostazol-free base can be attributed to the increased dissolution resulting from its sulfonic acid salt formation.

## Conclusion

In the present study, two novel cilostazol salts, cilostazol mesylate and cilostazol besylate, were prepared by acid addition reaction method. The two cilostazol salts exhibited good physicochemical properties, such as nonhygroscopicity, chemical stability, and processability, which make it suitable for the preparation of pharmaceutical formulations. Both cilostazol mesylate and cilostazol besylate significantly



**Figure 4** Mean plasma concentrations of cilostazol following oral administration of cilostazol-free base (●, n=8), cilostazol mesylate (○, n=8), and cilostazol besylate (▲, n=8) at a dose of 20 mg/kg cilostazol to rats. Vertical bars represent SD.

increased the dissolution rate and extent of drug release at a pH range of 1.2–6.8, and consequently increased the oral bioavailability in rats. The findings warrant further preclinical and clinical studies cilostazol mesylate, and cilostazol besylate at doses lower than that usually recommended dosage so that it can be established as an alternative to the marketed cilostazol tablet.

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**Table 2** Pharmacokinetic parameters (mean  $\pm$  SD) of cilostazol following oral administration of cilostazol-free base (20 mg/kg), cilostazol mesylate, and cilostazol besylate (equivalent to 20 mg/kg of cilostazol-free base) to rats

Parameters (unit)	Cilostazol-free base (n=8)	Cilostazol mesylate (n=8)	Cilostazol besylate (n=8)
Cilostazol			
$AUC_t$ ( $\mu\text{g min/mL}$ )	106 $\pm$ 26.0	304 $\pm$ 68.9*	312 $\pm$ 78.5*
Terminal half-life (min)	209 $\pm$ 68.6	232 $\pm$ 28.1	224 $\pm$ 49.2
$C_{max}$ ( $\mu\text{g/mL}$ )	0.365 $\pm$ 0.110	1.33 $\pm$ 0.311*	1.43 $\pm$ 0.340*
$T_{max}$ (min), median (range)	30 (15 $\pm$ 240)	15 (5 $\pm$ 30)	15 (5 $\pm$ 30)
$F$ (%)		287%	294%

**Notes:** \* $P < 0.05$ : cilostazol mesylate or cilostazol besylate vs cilostazol-free base.  $F$  (calculated as  $AUC_{t, \text{cilostazol salt}} / AUC_{t, \text{cilostazol-free base}} \times 100\%$ ).

**Abbreviations:**  $AUC_t$ , total area under the plasma concentration–time curve from time zero to time 720 minutes; min, minutes;  $C_{max}$ , peak plasma concentration;  $T_{max}$ , time to reach  $C_{max}$ ;  $F$ , relative bioavailability.

## Disclosure

The authors report no conflicts of interest in this work.

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